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PREVALENCE OF DIFFERENT TYPES OF THYROID DISORDERS IN A GROUP OF CHILDREN WITH DIABETES MELLITUS TYPE 1

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Abstract

Background&Aims: Thyroid disorders are frequently associated with diabetes in clinical practice. In type 1 diabetes, because autoimmune etiology it is often associated with autoimmune thyroid disease (chronic autoimmune thyroiditis, Basedow-Graves disease). The purpose of this study is to asses the prevalence of different types of thyroid disorders in a group of children with diabetes mellitus (DM) type 1. **Methods:** The studied group was represented by 83 children with diabetes mellitus type 1 (71 F and 12 M), aged between 7 and 17 years. Were used clinical, biochemical and imaging parameters. **Results:** Regarding the type of thyroid disease, prevailed ACT - 65.06% (87.03% F vs. 12.97% M, $p<0.001$, $X^2= 59.26$), followed by diffuse euthyroid goiter - 30.12% (80% F vs. 20% M, $p<0.001$, $X^2= 18$) and Graves-Basedow disease - 4.82% (100% F vs. 0% M, $p = 0.006$, $X^2= 8$). For each thyroid disease we determined the actual mean age, the onset mean age of thyroid disease and diabetes, the mean duration of diabetes and thyroid disease, mean BMI, glucose and HbA1c. We found significant differences between these three thyroid disease regarding actual age, onset age of diabetes, diabetes and thyroid disease duration. We don't found significant differences regarding BMI, blood glucose and HbA1c. **Conclusion:** In children with type 1 diabetes we found a net predominance of female and were prevailed autoimmune diseases such as part of the polyglandular autoimmune syndrome.

Keywords: Prevalence, children, thyroid disorders, diabetes mellitus type 1

Introduction

Thyroid disorders are frequently associated with diabetes in clinical practice. In type 1 diabetes, because autoimmune etiology it is often associated with autoimmune thyroid disease (chronic autoimmune thyroiditis, Basedow-Graves disease).

Thyroid disorders are common in the general population, their prevalence increases with age. Screening for thyroid disease is indicated in certain high-risk groups, such as infants and the elderly [Wu, 2000].

Hypothyroidism is the most common thyroid disease in the adult population and at older women. Usually they have autoimmune origin, presenting as atrophic primary hypothyroidism or Hashimoto thyroiditis. It may be also secondary to treatment with radioactive iodine or thyroid surgery. In rare cases, may occur secondary hypothyroidism to hypothalamic or pituitary disease [Wu, 2000].

By contrast, hyperthyroidism is less common, with a female / male ratio of 9/1. Graves' disease is the most common and usually affects young adults. Toxic multinodular goiter usually occurs in the elderly [Wu, 2000].

The patients with diabetes have a high prevalence of thyroid disease compared with non-diabetic population [Wu, 2000].

Because patients with organ specific autoimmune disease are at risk of developing other autoimmune diseases and thyroid disorders are more common in women, it is not surprising that 30% of women with type 1 diabetes present thyroid disorders. The rates of postpartum thyroiditis in diabetic patients are three times higher than in healthy women [Wu, 2000].

Type 1 diabetes is often associated with endocrine and systemic disease with autoimmune etiology such as Graves-Basedow disease, Hashimoto's thyroiditis, Addison's disease, celiac disease, pernicious anemia, myasthenia gravis, vitiligo, etc. [Cooper et al, 2003].

From people with type 1 diabetes, ≈ 1 in 100 patients will develop Graves' disease [De Block, 2000] and ≈ 1 in 20 patients are generally affected by hypothyroidism [De Block, 2000]. Frequency of DM type 1 association with hyperthyroidism and hypothyroidism varies from 3.2% to 4.6% and from 0.7% to 4% [Radaideh et al, 2003].

A private association of DM type 1 with hypo-or hyperthyroidism is characteristic for polyglandular autoimmune syndrome.

Material And Method

Method

Investigated Population

83 children with diabetes mellitus type 1 (71 F and 12 M), aged between 7 and 17 years represented the studied group. All the children present diabetes mellitus type 1.

Methods Of Investigation

The methods of investigation were represented by **clinical data -** case history, current status, **imagistic**- thyroid ultrasound, **biochemical** - ***for***

glycemic balance: fasting blood glucose, glycosylated hemoglobin, ***investigation of the thyroid gland***: TSH, FT_4, FT_3, thyroid antibodies.

Investigation of glycemic balance

Determination of plasma glucose was performed by enzyme technique with glucosooxidasis. Normal values were taken between 70 - 110 mg%; diabetes mellitus - values equal or over 126 mg%, impaired glucose tolerance - values between 110 - 125 mg% and the OGTT at 2 h between 140 - 200 mg% and impaired fasting glucose - values between 110 - 125 mg% and OGTT at 2 h under 140 mg%.

Determination of HbA1c was achieved through the DiaStat for measuring HbA1c reported to the total HbA.

Investigation of the thyroid gland

To determine ***the TSH level in plasma, the free fraction of triiodotironin (FT_3),*** and ***the plasma free fraction of thyroxin (FT_4)*** were performed a quantitative method ARCHITECT; witch is an immunological method, Chemilumnescent Microparticle Immunoassay (CMIA). Normal values were following: TSH = 0.465-4.68 Miu/ml, FT_3 = 3.69 -10.4 pmol/l, FT_4 = 10-28.2 pmol/l.

The immunological parameters were represented by autoimmune thyroid markers - antibodies (antiTPO and antiTg antibodies).

To determine ***serum levels of antiTPO antibodies*** it was used the kit AxSYM antiTPO, an immunological method (Microparticle Enzyme Immunoassay) (MEIA). Normal values: antiTPO antibodies <35 IU/ml.

To determine ***serum levels of antiTg antibodies*** it was used the kit AxSYM antiTg, a MEIA method as well (Microparticle Enzyme Immunoassay). Normal values: antiTg antibodies <55 IU/ml.

Thyroid ultrasound was performed in all cases and allowed us to measure thyroid volume, thyroid study and the changes in parenchyma's density.

An increased density, uniform, characterizes normal thyroid parenchyma easily distinguished from the neck muscles that are hypo dens.

Inflammatory processes and autoimmune pathology appears hypo dens**.** The scale was assessed as being discreet +, moderate ++ and marked +++.

In the autoimmune thyroid disease the parenchyma of the gland appears hypo dens.

In Grave's disease is seen an increased volume of the thyroid, hypoecogenity of different intensities with variable homogeneity in the thyroid parenchyma.

Chronic autoimmune thyroid disorder appears with a hypoecogenity of the parenchyma and normal or increased thyroid volume.

Statistical Analysis

For statistical analysis we used Microsoft Excel and POP Tools from Microsoft Office 2003 and EPI 2000 program. To measure the quantitative variables were determined media (M) and standard deviation (SD), and to assess the gender differences we used the unpaired t test and ANOVA test, considering statistically significant a $p < 0.05$.

Results And Discussion

The group of children was represented by 83 subjects aged between 7-17 years (Table I). All the subjects from the study had diabetes mellitus type 1.

Table I. Distribution by age and gender of children and adolescents group

Age	Cases number		Female		Male	
	n	%	n	%	n	%
0 - 4 years	-	-	-	-	-	-
5 - 9 years	2	2.4	2	100	-	-
10 – 14 years	32	38.56	22	68.75	10	31.25
15 – 17 years	49	59.04	47	95.92	2	4.08

Type 1 diabetes is the most common type of diabetes found in children and adolescents, represented the main cause of disease in Caucasians of northern Europe, especially in Scandinavian [Karvonen et al, 2000].

In the studied group, the gender distribution of the children was 5.9 / 1, represented by 71 girls (85.54%) and 12 boys (14.45%) (Fig.1). Compared to the literature, we found a net predominance of females, probably due to the DM type 1 association with thyroid disorders, frequent especially in women. The differences between male and female, on the prevalence of type 1 diabetes cases were highly significant ($X^2 = 83.33$, $p < 0.001$) in the group of children and adolescents.

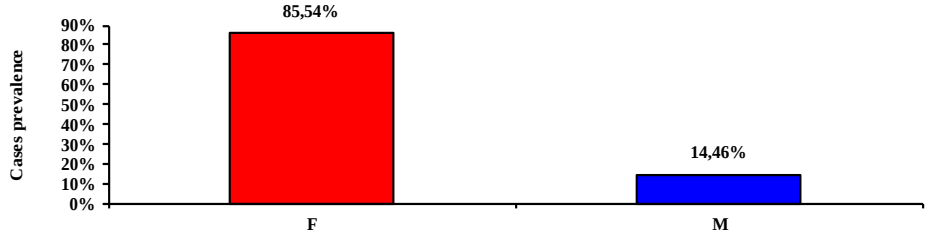

Fig 1. The gender distribution of the children

In general, type 1 diabetes affects boys and girls equally [Gale et al, 2001]. In populations with low risk of type 1 diabetes as Japanese and African-Americans, there is a preponderance of females, while in populations at high risk for type 1 diabetes there is a predominance of male patients [Steck et al, 2004].

In Europe, all the populations with an incidence of diabetes over 20/100000 (Sardinia, Great Britain, Finland, Italy, Norway etc.) has a predominance of male patients, while in the countries with a proportion of DM under 4.5/100000 (Baltic countries, Macedonia, Yugoslavia, Romania, etc.) is a predominance of females [Şerban et al, 2001].

In Romania there was a slight female predominance, which, overall, is not statistically significant, but that was highlighted by all studies conducted so far [Guja et al, 2004].

Regarding the type of thyroid disease, prevailed ACT, followed by euthyroid diffuse goiter and Graves-Basedow disease (Table 2). We note significance differences between ACT and euthyroid diffuse goiter ($p<0.001$, $X^2= 20.31$), between ACT and Graves-Basedow disease ($p<0.001$, $X^2= 66.25$) and euthyroid diffuse goiter and Graves-Basedow disease ($p<0.001$, $X^2= 18.43$).

Table 2. Distribution of children and adolescents group by the type of thyroid disease

Thyroid disorder type	Cases number		Group mean age (years)	Female		Male	
	n	%	medie ± DS	n	%	n	%
ACT	54	65.06	14 ± 2.4	47	87.03	7	12.97
Euthyroid difusse goiter	25	30.12	14 ± 1.93	20	80	5	20
Graves-Basedow disease	4	4.82	16 ± 0.5	4	100	-	-

Legend: ACT = autoimmune chronic thyroiditis

A number of studies have found that autoimmune chronic thyroiditis with or without goiter is the most common thyroid disorder occurring in patients with type 1 diabetes. It is approximate that 1 from 5 children with diabetes have antithyroid antibodies. The prevalence is 2-20 times higher in patients with type 1 diabetes than in the general population [Micle, 2000].

Other authors estimated the incidence of Hashimoto thyroiditis in patients with type 1 diabetes at 20% [Mărginean et al, 2000]. The results are contradictory, because other studies suggest that the prevalence of 21.6% in autoimmune thyroid disease may be overestimated [Kalicka – Kasperczyk et al, 2002].

In the U.S., at the Caucasian population with type 1 diabetes has been reported a prevalence of 50% of the disease [Kordonouri et al, 2002]. Hashimoto's thyroiditis is the most common cause of hypothyroidism in the

U.S. after the age of 6 years, with an estimated incidence of 1 3% in a sample of 5000 children aged between 11-18 years [Odeke et al, 2006].

A study from Australia shows that the incidence rate for thyroid disease in patients with type 1 diabetes is 0.9 / 100 patients / year [Glastras et al, 2005].

In the case of hyperthyroidism, the main cause in children is represented by Graves-Basedow disease. A U.S. study showed a prevalence of 30 cases per 100.000/year. Worldwide, it is estimated that Graves-Basedow disease represents between 60-90% of thyrotoxicosis cases in different regions of the world [Yeung et al, 2005].

A study from Israel shows that the main cause of thyrotoxicosis in children is the Graves-Basedow disease; this represents 10-15% of thyroid disorders in this age [Kraiem et al, 2001]. Thyroid hyperfunction of other etiology is much less common in patients with DM type 1, the proportion being 1%.

Regarding the gender distribution, we found a predominance of females in the study group, concordant aspect with the literature data, because thyroid disorders are more common in women.

Thus, in the case of ACT, a percentage of 87.03% cases were female and 12.97% male, with an F / M ratio of 6.7 / 1, the differences being highly significant ($X^2 = 59.26$, $p < 0.001$). In the literature, in the case of Hashimoto's thyroiditis it is shown that this is 10-15 times more common in women [Odeke et al, 2006].

In the case of euthyroid diffuse goiter, 80% of cases were female and 20% male, F / M ratio was 4/1, also highly significant differences ($X^2 = 18$, $p <0.001$). In the world, the euthyroid diffuse goiter frequency is about 5%, usually occurs around puberty and it is more common in females (F / M ratio = 1.2 - 4.3 / 1) [Lee et al, 2006].

In the case of Graves-Basedow disease all 4 patients were female. In the literature it is also show in this case a female predominance, the ratio F / M being 7-8/1 [Yeung et al, 2005].

A study in Greek on children with Graves-Basedow disease shows that female predominance is similar between children and adults (87% and 83% respectively) [Krassas et al, 2006].

Another study in the Czech Republic show a predominance of female subjects with autoimmune thyroid disease (68% vs. 32%) [Vondra et al, 2006].

In the study group, the onset mean age for Graves-Basedow disease was 15.75 ± 0.5 years, in the case of ACT 13.98 ± 2.46 years, and for euthyroid diffuses goiter 14.48 ± 1.93 years.

A study in Taiwan on 106 children shows that in the case of Graves-Basedow disease the onset minimum age was 3.36 years. The incidence of

disease increased progressively with age, with a peak at age 15 [Hung et al, 2006].

Another study in Thailand on 154 children with euthyroid diffuse goiter showed that the onset mean age was 12.8 ± 1.8 years [Jaruratanasirikul et al, 2000].

In Germany the study conducted in patients with autoimmune thyroiditis showed that the onset age for this was between 5.4 and 16.3 years, with a median of 11.3 years [Doeker et al, 2000].

Depending on the duration of thyroid disease, all 83 children from the study had an apparent duration of thyroid disease less than 5 years. A U.S. study on 1254 patients under 21 years has shown that autoimmune thyroid disorders are present in 4.2% of patients with type 1 diabetes of the study group. 39% from thyroid disease were diagnosed at 1 year after diabetes type1 and antiTPO antibodies were present in 90% of cases [Bilimoria et al, 2003].

Depending on the type of thyroid disease in the group of children, we made three groups:

- the group with Graves-Basedow disease
- the group with ACT
- the group with euthyroid diffuse goiter

At every group we determined the actual mean age, the onset mean age of thyroid disease and diabetes, mean duration of diabetes and thyroid disease, mean BMI, glucose and HbA1c (Table 3).

Significant differences between the 3 groups we obtain in the case of actual age, onset age of diabetes, thyroid disease and diabetes duration (Table 4).

Thus, in the case of onset age of diabetes the lower age was in the case of ACT group (5.42 ± 3.87 years) and the higher in the case of Graves-Basedow disease (16.75 ± 0.5 years).

The shortest duration of DM was found in patients with Graves-Basedow disease (0.25 ± 0.5 years) and the longest for ACT (9.07 ± 3.76 years).

In the case of thyroid disease duration the shortest was in the case of euthyroid diffuse goiter group, followed by the ACT group (0.48 ± 0.94 years) and Graves-Basedow disease group (1.25 ± 0.5 years).

We not obtained significant differences regarding BMI, blood glucose and HbA1c.

Table 3. Comparative data in function of type thyroid disease type in the group of children (mean ± SD)

Parameters	Graves–Basedow disease	Autoimmune chronic thyroiditis	Euthyroid difusse goiter
Actual age (years)	16.75 ± 0.5	14.46 ± 2.4	14.48 ± 1.93
Onset age of thyroid disease (years)	15.75 ± 0.5	13.98 ± 2.46	14.48 ± 1.93
Onset age of DM (years)	16.75 ± 0.5	5.42 ± 3.87	9.24 ± 4.52
DM duration (years)	0.25 ± 0.5	9.07 ± 3.76	5.16 ± 4.37
Thyroid disease duration (years)	1.25 ± 0.5	0.48 ± 0.94	0 ± 0
BMI (kg/m^2)	23.12 ± 0.97	20.63 ± 2.69	21.39 ± 4.19
Glycemia (mg%)	355 ± 309.5	154.72 ± 64.78	166.92 ± 67.68
HbA_{1c} (%)	13.72 ± 7.51	8.7 ± 2.06	10.37 ± 3.34

Table 4. Statistical differences (p) regarding thyroid disease parameters, depending on its type, in the group of children and adolescents

Parameters	Graves Basedow disease vs. ACT	Graves-Basedow disease vs. euthyroid difusse goiter	ACT vs. euthyroid difusse goiter
Actual age (years)	< 0.001	< 0.001	< 0.001
Onset age of thyroid disease (years)	0.0004	0.01	0.33
Onset age of DM (years)	< 0.001	< 0.001	0.0007
DM duration (years)	< 0.001	< 0.001	0.0003
Thyroid disease duration (years)	0.04	0.01	0.0004
BMI (kg/m^2)	0.0044	0.08	0.41
Glycemia (mg%)	0.28	0.31	0.45
HbA_{1c} (%)	0.27	0.44	0.02

Conclusion

In children with type 1 diabetes we found a net predominance of female and were prevailed autoimmune diseases such as part of the polyglandular autoimmune syndrome.

Because thyroid disorder occurring in a certain period of time after diabetes, it is necessary to determine the possibility of association of autoimmune diseases, especially for thyroid diseases (higher risk for those with autoimmune chronic thyroiditis for hypothyroidism) for all children with type 1 diabetes mellitus.

The methods recommended are the dosage of antithyroid antibodies at children and adolescents with type 1 diabetes at the onset of diabetes, or at the latest before puberty, and if they are positive, should be tested the thyroid

function and due the thyroid ultrasound to minimize the risk of undiagnosed hypothyroidism in young patients with type 1 diabetes.

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